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The efficacy of cyanoacrylate and beta-blockers in preventing gastric variceal rebleeds

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Abstract

Background: Esophageal and gastric varices are a frequent complication of patients with increased portal venous pressure. Gastic varice occurs and bleeds less frequently than esophageal varice in patients with portal hypertension. Bleeding of gastric varices, however, tends to be more severe and is associated with a higher rate of rebleeds and mortality. Currently, the treatment for preventing secondary gastric variceal hemorrhage includes transjuglar intrahepatic portosystemic shunting, band ligation propranolol and isosorbide mononitrate. Cyanoacrylate is the preferred treatment and has been effective in the treatment of actue gastric variceal hemorrhage worldwide but its use is limited in the United States. The use of cyanoacrylate in the preventing secondary gastric varices has not been well studied. It has been well documented that beta-blockers are effective in decreasing the incidence of secondary esophageal varices and is used empirically in prophylaxis of secondary gastric varices, without proof. The purpose of this systematic review is to determine whether the use of cyanoacrylate more effective than beta-blockers in preventing secondary gastric varices?

Methods: An exhaustive search was conducted using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science using the keywords: cyanoacrylate, beta-blocker, gastric varices and portal hypertension. Relevant articles were assessed for quality using GRADE. A search on the NIH clinical trials site reveals there are no trials comparing the efficacy of cyanoacrylate and beta-blockers in preventing secondary gastric varices.

Results: Two studies met the inclusion criteria and were included in this systematic review. A randomized controlled trial included 64 patients with portal hypertension and upper gastrointestinal bleeding who met the inclusion criteria. The study showed a statistically significant reduction in secondary gastric variceal hemorrhage with cyanoacrylate injection compared beta-blocker. A randomized control trial consisting of 41 patients with esophageal or gastric variceal bleeding were included in the study. Results demonstrated that repeat cyanoacrylate injections were associated with more complication compared to beta-blocker with similar rebleeding rates after 6 weeks.

Conclusion: Cyanoacrylate is effective in decreasing the incidence of gastroesphageal varice type II and isolated gastric varice type I rebleeds and mortality compared to beta-blockers. Beta-blockers demonstated a reduction in hepatic venous pressure gradient but there is no evidence that it prevents rebleeds from gastric varices. In addition, mixing cyanoacrylate and lipiodol resulted in more complication than cyanoacrylate alone. A strong recommendation can be made for the use of cyanoacrylate in both acute gastric variceal hemorrhage and secondary prophylaxis of gastric variceal bleed.

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Comparison: The efficacy of cyanoacrylate and beta-blockers in preventing gastric variceal rebleeds

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

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Biography

[Redacted for privacy]

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List of Abbreviations

GOV1……Gastroesophogeal Varice Type 1
GOV2.....Gastroesophogeal Varice Type 2
GRADE……....Grading of Recommendation, Assessment, Development and Evaluations
HVPG……...Heptic Venous Pressure Gradient
IGV1……Isolated Gastric Varice Type 1
IGV2……Isolated Gastric Varice Type 2
PHG……...Portal Hypertensive Gastropathy

Comparison: the efficacy of cyanoacrylate and beta-blocker in preventing gastric variceal rebleeds

BACKGROUND

Gastric and esophageal varices are complications of increased portal venous pressure. Gastric varices occur in about 20-25% of patients with portal hypertension.[1,2] Bleeding from gastric varices occur less frequently than esophageal varices[1]; however, the bleed tends to be more severe and is associated with a higher rate of mortality.[1,3,4] Furthermore, gastric varices have a higher rate of rebleeds, occurring about 34-89% after control of acute hemorrhage.[3,5,6]

The location of the gastric varices plays an important factor in the frequency and severity of bleeding.[5] Gastric varices are commonly classified by location using the Sarin classification. According to the classification system, there are four types of gastric varices: gastroesophageal varices type 1 (GOV1) are continuous with esophageal varices and extend 2 to 5 cm below the gastroesophageal junction; gastroesophageal varices type 2 (GOV2) are continuous with esophageal varices and extend into the cardia and fundus of the stomach; isolated gastric varices type 1 (IGV1)are varices that occur in the fundus of the stomach in the absence of esophageal varices; varices that occur in the gastric body, antrum or pylorus are called isolated gastric varices type 2 (IGV2).[1,2]

The treatment of gastric varices includes controlling the active bleeding and preventing secondary variceal hemorrhage. Currently, there are a number of treatment

options to control hemorrhaging but no standard approach has been agreed upon. Beta-blockers are effective in decreasing variceal pressure and esophageal varices in patients with portal hypertension.[10] Due to this, beta-blockers have been recommended empirically and used without evidence.[11] The use of beta-blockers in the treatment of gastric varices are not well studied. Early research has indicated that beta-blocker therapy alone or adjunctively does not improve rebleeding rates of gastric varices.[11,15]

The use of cyanoacrylate, another treatment option, is limited in the United States despite promising reports. International studies has demonstrated that cyanoacrylate therapy is safe and effective therapy in stabilizing acute hemorrhage.[8,14] In treating with cyanoacrylate, the hemorrhage is first visualized by an endoscope. Cyanoacrylate is then injected into the varix. Once the cyanoacrylate comes in contact with blood, an exothermic chain polymerization reaction occurs. Cyanoacrylate transforms from its original liquid form into a solid material, which physically occludes the vessels.[8,14] In laboratory setting, cyanoacrylate solidifies in 5-12 seconds after contact with human blood.[8,11] This transformation can be delayed with the use of lipiodol, a substances commonly used when treating gastric varices. This property allows the cyanoacrylate to be injected into the varix with ease. Lipiodol is also a radiopague contrast, which provides a non-invasive method to visualize the varix post-operatively.[8]

There is a low incidence of complications from cyanoacrylate therapy which includes sepsis, distant embolism, gastric ulcer, mesentery hematoma,

hemoperitoneum and abdominal infection.[7] Currently, the use of cyanoacrylate is limited to a number of centers in the United States under research protocol and is not approved by the Food and Drug Administration.[9] This review will investigate and compare the efficacy between cyanoacrylate and beta-blockers in the prophylaxis of secondary gastric variceal bleeds.

METHODS

A thorough search of available medical literature was conducted using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science using the keywords: cyanoacrylate, beta-blocker, gastric varices and portal hypertension. The search was refined to include only human articles. The references of the articles were further searched for relevant sources. Articles with primary data comparing the efficacy of cyanoacrylate and beta-blocker in the treatment of gastric varices were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).[12] A search on the NIH clinical trials site reveals there are no trials comparing the efficacy of cyanoacrylate and beta-blockers in preventing secondary gastric varices.

RESULTS

The initial results of the search yielded seven articles for review. Of these seven, two randomized controlled trials met the inclusion criteria.[11,13]

Mirsha et al study

This randomized controlled trial[11] investigated and compared the efficacy of beta-blocker and cyanoacrylate injection in the prevention of secondary gastric variceal bleeding. The study enrolled patients with gastric varices secondary to cirrhosis from August 2006 to March 2009. A total of 67 patients were enrolled, of which 64 participated and were randomized to receive either cyanoacrylate injection or beta-blocker. Patients who presented with active bleeds were treated with a combination of vasoactive drugs and a single injection of cyanoacrylate. After achieving homeostasis, follow-up was conducted on day 6 and continued thereafter. The primary outcomes were gastric variceal rebleed and death. Secondary outcomes included an increase or decrease in size of the gastric varices, appearance of new esophageal varices, and appearance or worsening of portal hypertensive gastropathy (PHG) and complications.[11]

Patients with gastroesphageal varices type 2 with eradicated esophageal varices or isolated gastric varices type 1 who bled from gastric varices who did not satisfy the exclusion criteria were included in the study. Patients were randomized using a sealed envelope technique. Allocation sequence remained known to the statistician. Investigators were blinded until intervention was assigned. Blinding was further achieved by concealing the group assignment from the doctors who evaluated the outcomes. [11]

The study consisted of 64 patients, 32 patients received cyanoacrylate injection and 32 received the non-selective beta-blocker, propranolol. Both groups were similar

in all baseline patient characteristics. All patients completed their assigned intervention with a median follow-up period of 26 months. Complete obturation with cyanoacrylate was achieved in all patients. All patients were compliant to the beta-blocker treatment with a mean dose of 160 mg per day.[11]

Treatment with cyanoacrylate demonstrated a significantly lower rate of recurrent variceal bleeding compared to beta-blocker treatment (15% compared to 55%, p=0.004). Three patients rebled in the cyanoacrylate treatment group (GOV2 (n=1), IGV1 (n=2)). Fifteen patients rebled in the beta-blocker group (GOV2 (n=12), IGV1 (n=3)). The study also showed a significant increase in frequency of rebleeding from GOV2 (p=0.005). A decrease in gastric variceal size from ~25 to ~5 mm was observed in all patients receiving cyanoacrylate injection (p<0.01). In contrast, 15 patients in the beta-blocker group had an increase in gastric variceal size ~25 to ~30 mm (p<0.01). Seven patients in the cyanoacrylate group and four patients in the beta-blocker group developed esophageal varices, none of which bled (p=0.302). Both treatment groups were similar in appearance or worsening of PHG (p=0.213). There was no significant difference in frequency of complication observed between the two groups (p=1). A significant increase in hepatic venous pressure gradient (HVPG) was observed in the cyanoacrylate group (p=0.001). None of the patients in the cyanoacrylate group showed a decrease in HVPG. The beta-blocker group demonstrated a decrease in HVPG, which was significant (p=0.003). A >20% reduction in HVPG was considered a response to treatment. Twelve patients responded to treatment. Five of those patients (GOV2 (n=4), IVG1 (n=1)) bled. Those who did not bleed had a mean decrease in HVPG of 30%

from baseline in comparison with a 22% decrease in those who bled. A significant difference in mortality was observed between the cyanoacrylate (n=1) and beta-blocker (n=8) group (p=0.016). Of the eight who died in the beta-blocker group, one patient responded to the beta-blocker treatment while the other patients did not (p=0.077).[11]

The authors found that a limitation to this study is including only patients with IGV1 or GOV2 types of gastric varices. This limits the applicability of the study to those two types of gastric varices. The authors conclude that cyanoacrylate is more effective in preventing secondary gastric variceal rebleeds and improve survival rates compared to beta-blocker treatment. Beta-blockers did not prevent gastric variceal rebleed despite a reduction in HVPG.[11]

Evrard et al study

In this randomized trial,[13] the authors investigated whether Histoacryl injections are useful for long-term treatment of esophageal varices. They compared Histoacryl obliteration with propranolol in preventing esophagogastric variceal rebleeds. From August 1995 to February 1999, seventy-one patients were admitted for upper digestive tract bleeding. Forty-one patients who presented with the first episode of bleeding (n=38) or second episode occurring at least 6 months after the first one (n=3) satisfied the inclusion criteria and were enrolled in the study. Thirty-one patients presented with esophageal varices and 10 patients had gastric varices. All patients were treated with Histoacryl at the time of admission to achieve hemostasis. An opaque sealed

envelope was used to randomly assign patients to either the Histoacryl (n=21) or propranolol group (n=20).[13]

The primary endpoints were rate of rebleeds, mortality and any complications, which were investigated at 6 weeks and after 6 weeks (the median follow-up duration of the Histoacryl group was 31.9 months and 23.2 months for the beta-blocker group). The authors agreed that the 6-week mark is an important time point for follow-up. They believed that this time point is when all consequences related to the bleeding event will manifest themselves. The authors performed an interim analysis after observing a higher complication rate in the Histoacryl group. The study was stopped early based on the results of the analysis.[13]

The data demonstrated no significant difference in rate of rebleeds at the 6-week mark. Five patients from the Histoacryl group rebled, 3 of which were gastric variceal rebleeds. Three patients in the beta-blocker group developed secondary variceal rebleeds, none of which were gastric in origin. Three patients died from the Histoacryl group compared to six in the beta-blocker group. Both groups had one patient who died from hemorrhage.

Median follow-up after 6-weeks for the Histoacryl group was 31.9 months (4.8-74.7) in contrast to the beta-blocker group which had a median follow-up of 23.2 months (3.0-70). No significant difference in rebleeds was observed between the two treatment groups. Six patients from the Histoacryl group experienced rebleeds, two that were secondary to gastric varices. Two patients in the beta-blocker group developed rebleeds, none located in the gastric region. The investigators did find that

the time between rebleeds was significantly delayed in the Histoacryl group. It was also observed that most of the patients who developed rebleeds in the Histoacryl group did not adhere to the recommended endoscopic follow-up schedule. No significant difference was observed in the overall mortality rate. One patient in the Histoacryl group died from hemorrhage in contrast to the beta-blocker group, which had no patient death from hemorrhage. Data analysis demonstrated a significantly higher incidence of complications in the Histoacryl group (n=10) compared to the beta-blocker group (n=2) ($p<0.02$). Most of the complications in the Histoacryl group occurred after esophageal injection (n=8).[13]

Evrard et al[13] concluded that the use of Histoacryl injection with the goal of eradicating esophagogastric varices were associated with more complications compared to beta-blocker treatment. They also determined that there were no significant differences in rate of rebleeds and long-term survival rates between the two groups. The authors speculated that the higher number of rebleeds in the Histoacryl group maybe related to non-adherence to the follow-up schedule. They also mentioned that the complications in the Histoacryl group were temporary and inconsequential, and severe complications such as embolism are infrequent. An interesting observation from the study was that all the rebleeds from gastric varices occurred in the Histoacryl group. The study was stopped early after results of an interim analysis. [13]

DISCUSSION

It has been reported that gastric varices occur in over 20% of patients with portal hypertension.[1 2] They are often present in patients with severe portal hypertension secondary to cirrhosis. Gastric varices are also associated with a higher rate of rebleeds after homeostasis.[3 5 6] Both studies[11,13] have differing conclusions on the efficacy of cyanoacrylate and beta-blocker treatment in the prophylaxis of secondary gastric variceal hemorrhage. The Mirshra study[11] demonstrated that cyanoacrylate maybe effective in preventing secondary gastric varices. The study included a multivariate analysis with variables that affect gastric variceal rebleeds. The analysis indicated that the treatment method, portal hypertensive gastropathy and size of gastric varix >20 mm independently correlated with gastric variceal rebleeds. Specifically, the cyanoacrylate group saw a decrease in varix size compared to the beta-blocker group, which saw an average increase in gastric variceal size of at least 5mm.[11] This is a noteworthy finding as it may lead to changes in current standards and guidelines. There was a also correlation with rebleeds and mortality in that only one patient in the cyanoacryte group died compared to eight patients in the beta-blocker group. We may need to reevaluate the efficacy of emipiric beta-blocker treatment. Moreover, the study also showed a significant increase in HVPG in the cyanoacrylate group. The occlusion of the bleeding varice redirects the flow of blood to other vessels. This could explain the increase incidence of esophageal varices seen in this group compared to the beta-blocker group.

In contrast, the study conducted by Evrard et al[13] demonstrated inconclusive results in regards to gastric rebleeding, but they do reaffirm the efficacy of

cyanoacrylate in controlling acute hemorrhage of gastric varices. They found no difference in rate of rebleeds and mortality between the two groups. The authors found that rebleeding from the Histoacryl group were from gastric varices. This observation may support the use of beta-blockers in the prevention of secondary gastric varices and should be further investigated.[13]

Both studies[11,13] have limitations and their findings need further investigation to fully understand the benefits of the two treatment options in gastric variceal therapy. The Mirshra study[11] was limited because small sample size and some lack of blinding. Since the comparison was between a procedure (cyanacylate injection) and an oral medication (propanolol), allocation concealment is inheritantly difficult. No mention of a double dummy technique was used. This study also did not use hemodynamic monitoring in measuring HVGP. The HVGP is estimated by measuring the pressure gradient between the wedged hepatic venous pressure and the free hepatic venous pressure. This study only included patients with either GOV2 or IVG2 varices. This may limit the application to those types of varices in the clinical setting.

The Evrard et al study[13] was even more limited in a number of aspects. The authors observed a high rate of complications in the Histoacryl group and performed an interim analysis. The study was terminated prematurely based on the results; this lead to a small sample size in the study. The complication mostly occurred in patients with esophageal varices who were treated with Histoacryl. This may limit the applicability of the study to those with esophageal varices. The authors observed an increasing rate of rebleeds long-term in the Histoacryl group. However, no definitive conclusions can be

made due to the small sample size. Patient compliance was another issue in this study since many patients didn't follow the scheduled endoscopic appointments, which may have influenced the rate of rebleeds in the Histoacryl group. Another possible explanation of the increase in complication is the use of lipiodol. As we know, mixing lipiodol with cyanoacrylate will delay the solidification, which can lead to complications such as distant embolism. This study[13] did not clarify which type of gastric varices included in the study. As mentioned earlier, the location of the gastric varices plays a role in the frequency of rebleeds and severity of bleeding.[5] This study can be strengthen by including more patient and clearly defining the type of gastric varices.

The GRADE quality assessment can be viewed on Table 1. The Mirsha et al study[11] was downgraded for the lack of patient blinding. Serious imprecision was also determined from the study. There was a small sample size, which weakens the study. Indirectness and inconsistency were not serious and no publication bias was observed in the study. This article was not upgraded. The overall quality for this article is low. After review, it was determined that the Evrard et al study[13] demonstrated serious limitations, indirectness and imprecision. The study had a small sample size and a lack of patient blinding. The primary outcome was not gastric rebleeding and the study was downgraded. The inconsistency of the study was not serious and no publication bias was determined. No upgrade was given. Based on the GRADE criteria, the overall quality for this article was very low. The overall combined quality of the studies reviewed is low based on the GRADE criteria

CONCLUSION

The Mirshra et al[11] study demonstrates that cyanoacrylate alone may be effective in preventing secondary gastric varice bleedings while the Evrard et al[13] study is inconclusive. More specifically, the evidence supports its use with patients with gastroesophageal varices type 2 and isolated gastric varices type 1. The benefit of this treatment may outweigh the risk of rare complications like cyanoacrylate embolism. Currently, cyanoacrylate is not considered first-line treatment in the United States for gastric varice hemorrhage. Based on the findings, cyanoacrylate should be considered and recommended when treating acute gastric hemorrhage. Due to the limitations of the article, we can only speculate the benefits of cyanoacrylate in the prevention of secondary gastric variceal hemorrhage. Further research with larger sample size is needed to fully understand the effectiveness of cyanoacrylate in the prevention of secondary gastric variceal rebleeds. Another interesting avenue of research is to compare the efficacy of cyanoacrylate alone or mixed with lipiodol.

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Table I. Characteristics of Reviewed Studies

Quality Assessment						
	Downgrade Criteria					*Quality*
Design	*Limitations*	*Indirectness*	*Imprecision*	*Inconsistency*	*Publication bias likely*	
Mirshra et al Study[11]						
RCT	Serious[a]	Not serious	Serious[c]	Not serious	No publication bias	Low
Evrard et al Study[13]						
RCT	Serious[a]	Serious[b]	Serious[c]	Not serious	No publication bias	Very Low

[a] lack of blinding

[b] primary outcome was not gastric rebleeding
[c] small sample sizes

Table II. Summary of Findings

	Number of Patients		*Outcomes*				
Study	*Treatment (total)*	*Placebo or no treatment (total)*	*Rebleeds*	*Mortality*	*Complications*		
Mirshra et al[11]	33	34	3	1	1		
Evrard et al[13]	18	14	2	2	3		

Figure I. Sarin Classification System